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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| EXAMINER |
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LUNDGREN, JEFFREY S

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| ART UNIT | PAPER NUMBER |
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1639

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|--|------------|---------------|
| 3 MONTHS | 04/20/2007 | PAPER |

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/821,662

Applicant(s)

BLANEY ET AL.

Examiner

Jeff Lundgren

Art Unit

1639

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 January 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 5, 50 and 57-69 is/are pending in the application.
- 4a) Of the above claim(s) 5, 58-60 and 64-69 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 50, 57 and 61-63 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date: _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Status of the Claims

Claims 5, 50, and 57-69 are pending; claims 5, 58-60 and 64-69 are withdrawn as being directed to a non-elected invention; claims 50, 57 and 61-63 are the subject of the Office Action below.

Claim Rejections - 35 USC § 112- Withdrawn

The rejection of claims 50 and 57 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn for the reasons of record.

Claim Rejections - 35 USC § 102 - Withdrawn

The rejection of claims 50 and 57 under 35 USC § 102(b) is withdrawn for the reasons of record.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Art Unit: 1639

Claims 50, 57 and 61-63, are rejected under 35 U.S.C. 103(a) as being unpatentable over Dauter *et al.*, *Acta Crystallographica D*57:239-249 (2001), in view of Congreve *et al.*, *Agnew. Chem. In. Ed.* 42:4479-4482 (2003), and/or Appleby *et al.*, *Structure* 7(6):629-641 (1999).

Claim 50 is directed to a method for designing a lead candidate compound towards a biological target molecule comprising, combining the target with a mixture comprising two compounds, wherein at least one of the compounds comprises a substituent having anomalous dispersion properties, followed by a structural determination, followed by the selection of "information" for the design of the lead candidate. Claim 57 further requires the use of the dispersion properties of the substituent.

Dauter teaches a method for determining the crystal structure of pepstatin-insensitive carboxyl proteinase (PCP), by soaking a PCP crystal in the presence of sodium bromide and lithium sulfate (see page 241, column 1). The sodium bromide has anomalous dispersion properties, which are used in the measurement. The structure of this target complex is solved (see page 248, column 1). As in claim 63, Dauter teaches the use of bromine. Also see the experimental and discussion of crystal forms I and II. As in claims 61 and 62, Dauter uses information relating to binding free energy, and molecular dynamics.

Although Dauter teaches the an improved analytical method for resolving protein ligand structures using anomalous dispersion properties, Dauter does not explicitly suggest that the method be used in a combinatorial approach for identifying a lead compound. As in claims 61 and 62, Dauter uses information relating to binding free energy, and molecular dynamics.

Congreve teaches dynamic combinatorial chemistry for as an approach with X-ray crystallography for finding target molecules, such as novel substrates, to host molecules, such as enzymes. Congreve summarizes the strategy and approach (page 4479-4480). As in claims 61 and 62, Congreve uses information relating to binding free energy, and molecular dynamics.

Appleby teaches MTAP catalyzes the reversible phosphorolysis of 5'-deoxy-5'-methylthioadenosine (MTA) to adenine and 5-methylthio-D-ribose-1-phosphate, and that MTA is a by-product of polyamine biosynthesis, which is essential for cell growth and proliferation. Because of its importance in coupling the purine salvage pathway to polyamine biosynthesis MTAP is a potential chemotherapeutic target. Accordingly, Appleby utilizes x-ray crystallography and determined the crystal structure of MTAP at 1.7 Å resolution using

Art Unit: 1639

multiwavelength anomalous diffraction phasing techniques. It is found that MTAP is a trimer comprised of three identical subunits. Each subunit consists of a single alpha/beta domain containing a central eight-stranded mixed beta sheet, a smaller five-stranded mixed beta sheet and six alpha helices. The native structure revealed the presence of an adenine molecule in the purine-binding site. The structure of MTAP with methylthioadenosine and sulfate ion soaked into the active site was also determined using diffraction data to 1.7 Å resolution. The overall quaternary structure and subunit topology of MTAP are similar to mammalian purine nucleoside phosphorylase (PNP). The structures of the MTAP-ligand complexes provide a map of the active site and suggest possible roles for specific residues in substrate binding and catalysis. Residues accounting for the differences in substrate specificity between MTAP and PNP are also identified. Appleby concludes that the detailed information about the structure and chemical nature of the MTAP active site will aid in the rational design of inhibitors of this potential chemotherapeutic target (i.e., lead candidates).

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Dauter, Congreve and Appleby are directed to the use of x-ray crystallography for structural analysis of protein-substrate interactions. One of ordinary skill in the art would have been motivated to utilize the improved technique and advances presented by Dauter for further practical applications as exemplified by Congreve and Appleby. Therefore the invention as whole was *prima facie* obvious at the time it was invented.

Conclusions

No claim is allowable.

If Applicants should amend the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (e.g., if the amendment is not supported *in ipso verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.


Art Unit: 1639

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeff Lundgren whose telephone number is 571-272-5541. The Examiner can normally be reached from 7:00 AM to 5:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, James Schultz, can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JSL



MARK L. SHIBUYA
PRIMARY EXAMINER